REMARKS

Summary of Office Action

Claims 49-57 are pending in the application. Applicants' specification was objected to for failing to include sequence identifiers. Claims 50 and 53 were objected to because of informalities. Claim 57 was rejected under 35 U.S.C. § 112, second paragraph. Claims 49-57 were rejected under 35 U.S.C. § 112, first paragraph. Claims 49-53 and 55-57 were rejected under 35 U.S.C. § 102 (a). Claims 50, 53, 54, and 56 were rejected under 35 U.S.C. § 103(a). Each of these issues is addressed as follows.

Objection under 37 C.F.R. § 1.821(d)

The Office has objected to Applicants' specification under 37 C.F.R. § 1.821(d) as failing to provide a sequence identifier for individual sequences identified on page 11 (lines 20-30) in Figs. 6-9. To address this issue, Applicants have amended the specification to include sequence identifiers for sequences found on page 11 (lines 20-30). In addition, Figs. 6-9 have been amended to include sequence identifiers. "Replacement Sheets" for Figs. 6-9 are enclosed. "Annotated Sheets Showing Changes" are also enclosed. No new matter has been added.

Informalities

Claims 50 and 53 were objected to on the grounds that the alternative operator "or" is repeated twice in each claim and should only be used once. The present amendment addresses this issue, and the objection to claims 50 and 53 should therefore be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 57 was rejected under 35 U.S.C. § 112, second paragraph as being indefinite for omitting essential steps. In particular, the Examiner asserts that the omitted steps are the return of the B-lymphocytes to the blood of the human because the preamble recites obtaining a monoclonal antibody from the blood of a human. For the following reasons, this rejection should be withdrawn.

Applicants submit that B-lymphocytes are part of the blood of a human and thus that

the method which comprises taking blood from a human, selecting B-lymphocytes therefrom, and obtaining antibodies from these B-lymphocytes is adequately referred to as a method for obtaining antibodies from the blood of a human. Nevertheless, to address the Examiner's concerns, claim 57 has been amended to include the steps of a) obtaining peripheral blood from a human, b) selecting, from the blood of the human, B-lymphocytes which produce antibodies which only partially inactivate the wild type FVIII protein, c) cloning the B-lymphocytes, and d) purifying of the monoclonal antibodies produced by the cloned B-lymphocytes.

Support for this amendment is found, for example, in the application as follows: Generally, the outline of the method of claim 57 is described in Example 1, page 19, line 26 to page 22, line 21.[1] Support for the introduction of the wording 'from B-lymphocytes obtained from the blood of' in the preamble as well as for step (a) is found on page 19, lines 27-28 ("Human monoclonal antibodies of the desired specificity and characteristics are obtained by transformation of *B-lymphocytes obtained from the peripheral blood of patients* suffering from hemophilia A or acquired hemophilia (emphasis added).") and on page 21, lines 24-25 (*"Peripheral blood samples were collected* from donors suffering from mild hemophilia and with inhibitors. *The peripheral blood mononuclear cells* (PBMC) were immortalized... (emphasis added)."); support for step (c) is found on page 20, lines 28-30 ("*B cells* (such as BO 2C11) producing anti-factor VIII antibodies *are then* expanded and *cloned* by limiting dilution as described for instance in *Current Protocols in Immunology*... (emphasis added).") and on page 21, lines 28-29 ("For example, one cell line, named Krix-1, was successfully cloned by limiting dilution (emphasis added)."); support for step (d) is found on page 21, lines 14-15 ("The thus selected *antibodies* are then produced in bulk culture and *purified* by affinity chromatography using methods well known to those skilled in the art (emphasis added).") and on page 21, lines 35-36 ("Human *monoclonal antibodies* were *purified* by adsorption on immobilized Protein A... (emphasis added).")

[1] Applicants note that all citations to Applicants' specification refer to PCT International Publication Number WO 01/04269 A1.

In view of the aforementioned comments and claim amendment, the § 112, second paragraph rejection of claim 57 should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph (new matter)

Claims 50 and 52-57 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. The Examiner states:

> (a) The phrase "scFv" claimed in claim 50, line 1, and 53 line, 6, (b) the phrase "having the capacity to partially inhibit fVIII activity" claimed in claims, 50, line 3, claim 53, line 7 1-2, claims 56-57, last line, (c) the phrase "80% identical to the amino acid sequence depicted in figure 8 and/or a variable light chain sequence being at least 80% identical to the amino acid sequence depicted in figure 9" claimed in claim 52, line 2-4 and (d) the phrase "having the capacity of partially inactivating factor VIII activity when said monoclonal antibody is in a physiological excess" claimed in claim 52, lines 5-6 represent a departure from the specification and the claims as originally filed.

For the following reasons, Applicants respectfully traverse this rejection.

scFVs

Support for the fact that scFVs were envisaged in the specification as filed is found, for example, on page 1, lines 6-7 ("The present invention relates to novel cell lines and to ligands, namely human and/or humanized monoclonal antibodies, as well as fragments such as Fab, Fab', F(ab')2, *scFv,* single variable domains, complementarity determining regions, derivatives, homologs and combinations thereof, obtainable from the said cell lines (emphasis added).") and on page 13, lines 10-13 ("The present invention also provides fragments of any of the above monoclonal antibodies such as Fab, Fab', F(ab')2, *scFv,* CDR's, single variable domains as well as derivatives, homologs and combinations of these (emphasis added).")

Having the capacity to partially inhibit fVIII activity

The phrase "having the capacity to partially inhibit fVIII activity" is supported by the description at least page 8, lines 14-17 ("Preferably, these ligands, being other than polyclonal antibodies, provide a therapeutically useful plateau level by *only partially inhibiting* the function of the targeted factor so that a residual activity of the factor remains even when the ligand is used in a molar excess (emphasis added).") and on page 10, line 37 through page 11, line 2 ("The ligands may be anti-factor VIII antibodies or antibodies against a factor VIII complex, in particular human or human hybrid monoclonal antibodies which bind to factor VIII or a factor VIII complex and *at least partially inhibit the activity of factor VIII* (emphasis added).")

80% identical to the amino acid sequence depicted in figure 8

Support for "80% identical to the amino acid sequence depicted in figure 8" and a variable light chain sequence being at least 80% identical to the amino acid sequence depicted in figure 9" is found in the specification, for example, at page 7, lines 29-32 ("The present invention is related to new *ligands,* namely new monoclonal human or humanized antibodies, fragments, derivatives and *homologs* thereof, which bind to a factor involved in hemostasis, in particular to a factor or factors of the coagulation cascade and more in particular bind to factor VIII or a complex thereof (emphasis added).") in combination with page 12, lines 18-20: ("Where the ligands in accordance with the present invention include amino acid sequences, homology *may include having at least 80%,* more preferably 90% and most preferably 95% amino acid *sequence identity with the relevant ligand* (emphasis added).") and at page 11, lines 20-22 ("Figs. 6 and 8 show *amino acid sequences* (the lower lines) and nucleotide sequences (upper lines) *for the variable regions* V_H of the heavy chains of BO2C11 and the KRIX 1 monoclonal antibodies... (emphasis added)") and page 11, lines 26-28 ("Figs. 7 and 9 show *amino acid sequences* (the lower lines) and nucleotide sequences (upper lines)for *the variable regions VL* of the light chains of BO2C11 and the KRIX 1 monoclonal antibodies, respectively (emphasis added).) It is further submitted that it is clear from the specification at least from the section on page 7, lines 29-32 (cited above), that the term 'ligands' is used in the specification to refer to antibodies. Applicants

further submit that this section on page 7, lines 29-32 clearly refers to fragments of monoclonal antibodies as 'ligands' and thus, accordingly the homologs of these fragments, so that the section of the application relating to homologs on page 12, lines 18-20 (cited above) clearly applies to these fragments. It will be clear to the skilled person that the variable heavy and light chains are fragments of antibodies.

Nevertheless, and without acquiescence of the Examiner's objections, claim 52 has been amended to refer to "the complementarity determining regions of the antibody." Support for this amendment can be found on page 16, lines 9-12: ("The degree of homology with the said monoclonal antibody is preferably at least 80%, more preferably 90% and most preferably *95%,* and the homology is preferably particularly *in respect to the complementarity determining regions of the antibody* (emphasis added).")

Having the capacity of partially inactivity factor VIII activity when said monoclonal antibody is physiological excess

Support for the phrase "having the capacity of partially inactivating factor VIII activity when said monoclonal antibody is in physiological excess can be found on in the claim 3 as filed. However, to improve the consistency with the application, the term "physiological excess" has been replaced by "molar excess" as used throughout the specification, such as on page 8, lines 12-15 ("Preferably, these ligands, being other than polyclonal antibodies, provide a therapeutically useful plateau level by only partially inhibiting the function of the targeted factor so that a residual activity of the factor remains even *when the ligand is used in a molar excess* (emphasis added).")

Rejection under 35 U.S.C. § 112, first paragraph (biological deposit)

Applicants note that hybridoma LMBP5089CB was deposited under the terms of the Budapest Treaty as identified on the receipt of the Belgian Coordinated Collections of Microorganisms (BCCM™), which was included in the application as filed and acknowledged by the Office. This description, as required under the rules, clearly provides the accession number for the deposit, the date of the deposit, a description of the deposited biological material, and the name and address of the depository. It is therefore

submitted that page 13 (lines 22-26) clearly indicates the accession number (LMBP 5089CB), the date of the original deposit to be July 1, 1999 and also provides the address of the International Depository Authority. Nevertheless, to advance prosecution, Applicants enclose a statement by co-inventor Dr. Marc G. Jacquemin, with regard to the term of this deposit.

Rejection under § 112, first paragraph (enablement/written description)

Claims 52-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Examiner further asserts that Applicants' claims contain subject matter which was not described in the specification in a such a way to reasonably convey that the inventors had possession of the claimed invention. For the following reasons, these rejections should be withdrawn.

In maintaining the rejection, the Examiner states:

> There is no described or art-recognized correlation or relationship between the structure of the invention, the modified C1 domain of the FVIII and its partial[] function, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of variants C1 domain of FVIII which retain the features essential to the instant invention.

Applicants disagree.

Applicants first point out this basis of the rejection is irrelevant to claims 52 to 55 because the modification of the C1 domain is not an element of the claims.

Applicants further submit that there is a correlation between the ability of the antibodies of the invention to bind the C1 domain of FVIII and the partial inhibition of FVIII by the claimed variants. The skilled person can establish, by simple testing of binding of the antibodies to the C1 domain of FVIII, which variants are encompassed within the claims.

In addition, Applicants note that the modified FVIII function or C1 domain is only required for the method of the invention relating to the in vivo production of the antibodies

of the invention or their isolation from human patients (claims 56-57). Indeed, it will be understood by the skilled person that healthy animals, having non-modified FVIII circulating in their body, will not easily develop antibodies to FVIII upon immunization with FVIII. However, as detailed in the specification on page 9, lines 32 to 37 animals which have a partially functionally modified FVIII in their circulation, will respond to injected native FVIII as a foreign protein, and thus generate antibodies against this native FVIII. More particularly, to obtain antibodies against the C1 domain of FVIII, it is of interest to immunize animals having a defective or variant C1 domain so that the wild-type C1 domain of FVIII is recognized as foreign when used for immunization and antibodies against this domain are produced.

The Examiner further states:

> One of skill in the art would not envisage, based on the instant disclosure, the claimed genus of monoclonal antibodies comprising a variable heavy sequence being at least 80% identical to the amino acid sequence depicted in figure 8 and/or a variable light chain sequence being at least 80% identical to the amino acid sequence depicted in figure 9 which retain the partially inactivating factor VIII activity.

Applicants respectfully disagree with this assertion.

In connection with claim 52, Applicants respectfully assert that further characterization of the claimed antibodies or fragments thereof is not necessary to distinguish the claimed antibodies that fall within the scope of the claims. As stated in the Written Description Guidelines (66 FR 1106),

> [f]actors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

The claimed antibodies are distinguished from other antibodies (or fragments thereof) by both (i) the structural characteristic of a variable heavy sequence being at least 80% identical to the amino acid sequence of the complementarity determining regions depicted in figure 8 and a variable light chain sequence being at least 80% identical to the amino acid sequence of the complementarity determining regions depicted in figure 9 and (2) the specific functional characteristic of binding the C1 domain of Factor VIII. Based on Applicants' disclosure of these properties and routine assays for determining whether a particular composition has these properties, one skilled in the art would appreciate that Applicants were in possession of the claimed antibodies (and fragments) and that one of skill in the art would envisage, based on Applicants' disclosure, the claimed genus of monoclonal antibodies.

The Examiner also contends that "undue experimentation would be required to produce the antibodies of the invention commensurate with the scope of the invention of the claims from the written disclosure alone."

In response, Applicants first point out that the first paragraph of 35 U.S.C. § 112 requires that the specification of a patent enable a person skilled in the art to make and use the claimed invention. "Patents ... are written to enable those skilled in the art to practice the invention." *Lindemann Machinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1985). A patent specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without "undue experimentation." *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed Cir. 1988); *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 954 (1987) ("A patent need not teach, and preferably omits, what is well known in the art.") The Patent Office bears the burden of clearly and convincingly proving facts showing that the claims are not enabled. *E.g.*, *In re Marzocchi*, 439 F.2d 220

(CCPA 1971) ("[A] specification disclosure which contains a teaching in the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support (emphasis original).")

Applicants' written specification fully enables the practice of their claimed invention because the monoclonal antibodies or antigen-binding fragments thereof needed to practice the claimed methods are readily made using materials and routine methods that were known in the art and described in their specification. In view of these teachings and the state of the art, the Examiner contends that the claims are unpatentable for lack of enablement. In particular, the Examiner posits that the specification does not enable an ordinarily skilled artisan to practice the full scope of the claims because "undue experimentation would be required to produce the antibodies of the invention commensurate with the scope of the claims from the written disclosure alone." In support, the Examiner points to evidence – Rudikoff et al. (*Single amino acid substitution altering antigen-binding specificity*, Proc. Natl. Acad. Sci. 79: 1979-1983, 1982) – which he believes shows that one of ordinary skill could produce other antibodies falling within the scope of Applicants' claims only after undue experimentation, and therefore contends that this evidence supports nonenablement.

Applicants note that "enablement is not precluded by the necessity for some experimentation such as routine screening." *Wands*, 858 F.2d 731, 740. Applicants' written specification provides considerable direction and guidance on how to practice their invention and presents several working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed for the production of the antibodies or antigen-binding fragments used in the claimed methods were well known. Nonetheless, to challenge the teachings of Applicants' specification, the Examiner relies on Rudikoff for allegedly teaching that "a single alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in loss of antigen-binding function." From this teaching, the Examiner concludes that it is "unlikely that the

antibody defined by the claims ... would have the required binding function."

As an initial matter, Applicants note that Rudikoff, contrary to the Examiner's assertion, does not stand for such a broad proposition. Rudikoff explicitly, at page 1982 (col. 1), states: "It is clear that all such substitutions [single amino acid substitutions] need not and probably do not affect antigen binding." In view of this statement alone, the Examiner's reliance on Rudikoff is misplaced. Moreover, dependence on Rudikoff is inappropriate, in this case, given that "practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." *Wands*, 858 F.2d 731, 740. Applicants' specification clearly teaches one skilled in the art methods to screen for antibodies and antigen-binding fragments that bind the C1 domain of Factor VIII. Such screening is routine and cannot constitute undue experimentation. In addition, given that Applicants' specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention, there is again no undue experimentation.

The Examiner provides no evidence that conclusively shows that one of ordinary skill following the techniques disclosed in the specification could produce other antibodies requiring the claimed characteristics only after undue experimentation. Because it is imperative when attempting to prove lack of enablement to show that one of ordinary skill in the art would be unable to make the claimed invention without undue experimentation, the Examiner's evidence concerning Applicants' specification, with respect to identifying antibodies or antigen-binding fragments thereof that bind to the C1 domain of Factor VIII, is insufficient as a matter of law.

With respect to claim 52, the Examiner points out that the antibody fragments are "not limited to antibody fragments that have the capacity of partially inactivating factor VIII activity." To address this issue, claim 52 has been amended to require that the "fragment thereof binding the C1 domain of fVIII." The claim has also been amended to relate to antibodies which have at least 80% sequence identity with the Krix-1 antibody in the CDR regions. Accordingly, the skilled artisan cannot only envision which variations to contemplate but also how to identify those antibodies that fall within the scope of the

claims.

The Examiner also alleges that, with respect to claim 56 and 57, it is "[u]nclear which mutation in the C1 domain of the FVIII would lead to partially function of the antibody." The Examiner states:

> The specification fails to provide sufficient guidance regarding the changes and modifications that can be made to the C1 domain of the FVIII protein while retaining function. The specification fails to provide sufficient guidance as to which amino acid of the C1 domain of the FVIII protein is essential for maintaining its biological activity and which changes can be made in the structure of the C1 domain of the FVIII protein and still maintain the same function. Table 1 of the specification provides modifications in the FVIII domains (not only C1 domain), wherein KRIX1 inhibited the activity of all mutated factor VIII molecules tested except those carrying the mutation Arg2150His.

Applicants disagree.

The modified FVIII function or C1 domain is discussed above. In addition, Applicants point out that the additional feature which specifies that the FVIII protein is at least partially active is merely for practical reasons, as upon complete inactivation of FVIII, the survival of the animal or human involved is severely compromised. It is submitted however that, as will be understood by the skilled person, for the method of claim 56 which relates to generating anti-FVIII antibodies in animals, the only relevant requirement for the modification is that it is with respect to the wild-type protein, so as to increase, as detailed above, the chances of obtaining an immunogenic response to the wild-type protein. Claims 56 has been amended accordingly.

With regard to claim 57, which relates to a method for obtaining antibodies from human patients having circulating anti-FVIII antibodies, Applicants submit that individuals falling within the scope of the claims are identified based on the partial function of the FVIII protein which results in a pathological condition. The method of the invention thus encompasses identifying within the patients suffering from defective FVIII function, those patients whereby the defective function is due to a modification in the C1 domain. It is submitted that every modification of the C1 domain which results in defective FVIII function

is indicative of the fact that wildtype FVIII will be recognized as foreign and that upon administration of FVIII to these patients, antibodies to wildtype FVIII, more particularly to the C1 domain of FVIII will be produced (as this will be recognized as significantly different from the endogenous FVIII having a modified Cl domain).

In addition, Applicants point out that the Examiner's assertion regarding Table 1 is incorrect. Table 1 provides at least 10 mutations in C1 domain which result in reduced (i.e., partial) factor VIII activity. Table 1 on page 24 of the application as filed, for example, provides a list of mutation in FVIII (column 1) and their effect on factor VIII activity (column 2), whereby 1 IU/ml is to be considered the natural activity of factor VIII. This list also includes mutations in the C1 domain, which spans from AA2020 to AA2172 in factor VIII, more particularly Leu2052Phe, Asp2074Gly, Thre2086Ile, Ile2098Ser, Phe2101Leu, As2129Ser, Arg2150His, Pro2153Gln and Arg2159Leu, each of which demonstrate decreased, but still partial FVIII activity.

With regard to the specific objection that clam 52, on page 6 last paragraph of the office action, it is believed that the indication that the CDR regions of the variable regions should have at least 80% sequence identity with the Krix-1 antibody should overcome these comments. Indeed this limits the scope of the claim to those that are essentially related to Krix-1. It is submitted that it is within the ambit of the skilled person to make slight variations in the CDRs of a monoclonal antibody, without affecting binding affinity. Indeed, on the issue of claim breadth, Applicants note that limiting the claims along the line suggested by the Office would unacceptably narrow the coverage to specific antibody disclosed in the examples found in Applicants' specification. A potential infringer would easily avoid infringement by simply appropriating Applicants' invention using routine methods well known when Applicants field their application. Given the inventors' significant discovery and disclosure such claims would not adequately protect the inventors. See *In re Goffe* 542 F.2d 564, 567, 191 U.S.P.Q.2d 429, 431 (C.C.P.A. 1976) ("[T]o provide effective incentives, claims must protect adequately inventors. To demand that the first to disclose shall limit [his or her] claims to what [he or she] has found will work ... would not serve the constitutional purpose of promoting progress in the useful arts.")

The Examiner further contends that Applicants' specification does not teach how

to make and use the polypeptides of the invention. In particular, the Examiner states:

> The instant fact pattern fails to indicate that a representative number of structurally related KRIX-1 amino acid molecules [are] disclosed. The artisan would not have known how to make them. The artisan would not know the identity of a reasonable number of representative KRIX-1 falling within the scope of the instant claim and consequently would not have known how to make them.

Applicants disagree.

Applicants' specification certainly enables the claimed antibodies and fragments. Moreover, Applicants' disclosure provides specific and useful teachings regarding the claimed antibodies and fragments within the scope of the claims. By the filing date of Applicants' application, antibody production and screening was so well known that they had become routine technology, and technicians of ordinary skill in this art could make and use them by that time without undue experimentation. No evidence has been presented to suggest otherwise.

Applicants' specification, as discussed above, clearly enables one of ordinary skill in the art to practice the full scope of the claimed invention. Applicants disclose KRIX 1 and C1 binding fragments thereof. Applicants further sequenced the variable domains of KRIX 1 and disclose the VH and VL regions of the antibody including the three CDRs for each of the short and long chains. In view of this disclosure and using the artisan's knowledge of the prior art and routine experimentation, additional antibodies and their fragments can be made and used. Accordingly, there can be no question that Applicants' specification is commensurate in scope with the claims under consideration.

With respect to the claimed pharmaceutical compositions, the Examiner states:

> [T]he claimed pharmaceutical composition is not limited to the partial reduction of fVIII activity, but recites the use for prevention or treatment of any disorder of hemostasis and resulting pathological condition in mammals. However, an effective protocol for the prevention and treatment of disorders of hemostasis and resulting pathologic conditions in mammals is subject to a number of factors which enter the picture beyond simply the administration of the therapeutic

> composition in an acceptable formulation. Demonstrating partial inhibition of fVIII by KRIX-1 antibody cannot alone support predictability for preventing and treating any disorder of hemostasis and resulting pathologic conditions through administration of the appropriate formulation.

This element of the § 112, first paragraph, rejection, appears to question the utility, rather than the enablement, of the invention. The M.P.E.P. at § 2107.01-III(B) states: "Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being 'wrong,' even when there may be reason to believe that the assertion is not entirely accurate." Nonetheless, while the Office has stated that "an effective protocol for the prevention and treatment of disorders of hemostasis and resulting pathologic conditions in mammals is subject to a number of factors," no evidence has been provided that may be relied upon to reach this conclusion, as is required by the M.P.E.P. Applicants submit that, absent data or evidence to the contrary provided by the Examiner, it is credible that administration of a monoclonal antibody produced by the cell line named KRIX 1 (or a fragment thereof) will prevent or treat a thrombotic pathological condition in a mammal (claims 53-55 as amended).

Applicants' asserted utility is credible. Applicants assert that the present invention provides antibodies (or fragments thereof) that bind the C1 domain of FVIII and partially inhibits FVIII activity that can be used directly as a therapeutic. The present invention is based on Applicants' discovery of an antibody that binds the C1 domain of FVIII and partially inhibits FVIII activity. Applicants' specification, for example, teaches production of an antibody, referred to as KRIX1, from hemophilia A patients (Example 1) having the claimed characteristics. In addition to demonstrating binding of the C1 domain of FVIII and partial inhibition of FVIII activity, Applicants demonstrated that administration of the antibody to hamsters reduced mean thrombus size greater than 50% (Example 7). Applicants' specification therefore demonstrates several important facts about the claimed pharmaceutical compositions that are the basis for Applicants' asserted utility. The disclosed ability of the therapeutic antibodies (or fragments thereof) to partially inhibit FVIII activity strongly supports the specific utility of the monoclonal antibody produced by KRIX-1, C1 binding fragments of such antibody, and any antibody (or fragment) that binds the C1

domain of FVIII as therapeutics for preventing or treating thrombotic pathological conditions in a mammal.

Moreover, from Applicants' specification, a skilled artisan would clearly understand that inhibiting FVIII function is desirable for the treatment of diseases associated with any number of thrombotic pathological conditions including pulmonary embolism, coronary artery disease, peripheral artery disease, arterial thrombosis arterial restenosis, venous thrombosis, and atherosclerosis. For example, as outlined in the specification, deep vein thrombosis ("DVT") is caused by hemostasis, and thus DVT can be treated by antagonizing FVIII activity at a level that allows sufficient hemostasis to prevent bleeding but protects from pathologic thrombus formation. Because FVIII is required for clotting, administration of Applicants' therapeutic antibodies, like the administration of other thrombolytic agents such as t-PA, aspirin, or streptokinase, to a subject with a blood coagulation disorder would be expected to reduce the adverse effects caused by coagulation and clotting. Applicants note that these asserted disease associations are neither general in nature, nor are they inconsistent with what one skilled in the art would expect for the specific disease involvement of the therapeutic antibodies (or fragments thereof) based on Applicants' disclosure of its ability to bind the C1 domain of FVIII and its ability to partially inhibit FVIII activity.

It is noted that all assertions must be shown to be incredible for this rejection to stand. The burden is on the Examiner to provide a detailed, reasoned explanation for the rejection, and it is Applicants' understanding that the Examiner will either provide a rebuttal for each of Applicants' assertions of utility or will reverse these rejections in view of the clarifications that have been provided during prosecution.

With respect to using the claimed pharmaceutical compositions for preventing disorders of hemostasis and resulting pathologic conditions, the Examiner further asserts that Applicants' specification does not provide sufficient teachings regarding (1) how it can be assessed that prevention was achieved after the administration of the therapeutic composition of the invention and (2) what is the target population that needs the prevention treatment. Applicants disagree.

Applicants' pharmaceutical compositions, as described in their specification, aim to

inhibit the formation of blood clots and to prevent pathologic consequences resulting from the formation of such blood clots. It was well known at the time Applicants filed their application that anticoagulant therapy limits or prevents extension of formed clots or prevents the formation of new ones. In the case of a myocardial infarction, for example, a blood clot typically forms inside a coronary artery that already has been narrowed by atherosclerosis. Applicants' pharmaceutical compositions are administered, for example, to prevent further blood clotting. (See, for example, Applicants' specification at page 2 (lines 13-26), page 10 (lines 7-19), and page 18 (lines 1-8).)

Applicants' pharmaceutical compositions, in another context, are also be used to prevent and treat, for example, deep vein thrombosis, a condition in which harmful blood clots form in the blood vessels of the legs. In deep vein thrombosis a portion of the leg blood clot can break off and travel to the lungs where it can become lodged in the blood vessels of the lungs, causing a condition called pulmonary embolism. A pulmonary embolism can case sudden death. Patients at risk for developing deep vein thrombosis include, for example, those having surgery which can trigger the formation of blood clots. Applicants' compositions may therefore be used for several days, for example, after surgery, while a patient is unable to walk, preventing deep vein thrombosis. (See, for example, Applicants' specification at page 1 (lines 21-23), page 10 (lines 7-19) and page 18 (lines 1-8)).

Moreover, it was well known in the art how to to manage and monitor patients receiving antithrombotic therapies at the time the application was filed. This includes assessment of efficacy and achievement of therapeutic goals. Thus, for example, as was known in the art, it is extremely important to regularly evaluate a patient's response to an anticoagulant therapy such as Applicants' pharmaceutical composition. This ensures that excess bleeding does not occur due to improper dosing of the composition. Standard methods were known in the art for making such determinations, for example, by measuring FVIII levels or antibody titer. This blood test enables a physician to adjust the dose of Applicants' composition to provide optimal anticoagulation benefits without inducing serious bleeding. Such routine dosing and testing was well known when Applicants' application was filed and was well within the skill of the art.

Finally, Applicants point out that no evidence currently made of record in this case establishes a basis for doubting the objective truth of the statements found in Applicants' specification regarding the routine nature of making and using the claimed antibodies and fragments thereof and compositions. The Examiner is required to provide persuasive reasons for doubting that detailed guidance and examples of the specification would not be adequate to allow someone to practice the invention. As stated in *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971):

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope used in describing and defining the subject matter sought to be patented must be taken in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

No documentary evidence, however, is made of record in this case supports the Examiner's assertion of uncertainty about making and using the claimed antibodies, their fragments, and compositions. In contrast, Applicants have demonstrated that ligands that bind the C1 domain of FVIII and partially inactivate its activity can be isolated, cloned, and expressed. Furthermore, given Applicants' success, the Office's contention regarding enablement is unreasonable and cannot support its lack of enablement rejection. In a situation such as this one, *Marzocchi* compels withdrawal of the enablement rejection.

Rejections under 35 U.S.C. § 102 (a)

Claims 56-57 stand rejected under 35 U.S.C. § 102 (a) as being anticipated by Jacquemin et al. (Blood 92:496-506). Claims 49-53, 55, and 57 stand rejected under 35 U.S.C. § 102 (a) as being anticipated by Jacquemin (Gilles) et al. (Blood 92:pp710). The following reasons there rejections should be withdrawn.[2]

[2] The Office Action refers to Jacquemin (Gilles), which on p. 710 of Blood (vol. 92) includes Jacquemin et al, Mutation ARG 2150 → HIS in the Factor VIII C1 Domain Alters the Binding of Factor VIII to von Willebrand Factor and is Responsible for a Mild Hemophilia A Phenotype (Abstract #2917) and Gilles et al, The Arg 2150 His Mutation Within the Factor VIII C1 Domain Eliminates a B Cell Epitope That is Present Only on Factor VIII von Willebrand Factor Complexes (Abstract #2919).

Applicants first point that Jacquemin et al. (Blood 92:496-506) relates to antibodies that recognize the C2 domain of FVIII, not the C1 domain as presently required by the claimed method. Indeed, as stated in the abstract, "it [BO2C11] completely inhibits the procaogulant activity of native and activated fVIII ..." The claim methods specifically require selecting or obtaining antibodies which only partially inactivate the wild type FVIII protein. Jacquemin et al. (Blood 92:496-506) therefore cannot anticipate the currently claimed invention.

In addition, in connection with Jacquemin et al. (Blood 92:710 (Abstract #2917)) or Gilles et al. (Blood 92:710 (Abstract #2919)) references, Applicants submit a Declaration by Dr. Marc G. Jacquemin stating that any description of the present invention in these publications was the contribution of the present inventors, Marc G. Jacquemin and Jean-Marie Saint-Remy, alone. As the cited Jacquemin et al. (Blood 92:710 (Abstract #2917)) or Gilles et al. (Blood 92:710 (Abstract #2919)) references are not prior art under 35 U.S.C. § 102 (a), this basis of rejection should also be withdrawn.

Rejections under 35 U.S.C. § 103 (a)

Claim 56 stands rejected under 35 U.S.C. § 103 (a) as unpatentable over Jacquemin (Gilles) et al. or Jacquemin et al. (Blood, 92:496-506) each in view of U.S. Patent No. 6,602,015. Claims 50 and 53 stand rejected as unpatentable over Jacquemin (Gilles) et al. in view of Owens et al. (1994). Claim 54 is also rejected as unpatentable over Jacquemin (Gilles) et al. in view of U.S. Patent No. 6,127,337.

In reply to the rejection of claim 56, Applicants first direct the Examiner's attention to the above remarks in connection with Jacquemin et al. (Blood 92:496-506), where it is stated that this reference fails to teach the claimed invention. In addition, the secondary reference, U.S. Patent No. 6,602,015, cannot support this rejection alone, and the rejection of claim 56 may therefore be withdrawn.

The rejection of claims 50, 53, 54, and 56 over Jacquemin (Gilles) et al. may also be withdrawn. Applicants again direct the Examiner's attention to the accompanying Declaration of Dr. Marc G. Jacquemin, where it is stated that any description of the present invention in the Jacquemin (Gilles) et al. (Blood 92:710 (Abstract #2917) or Gilles et al. (Blood 92:710 (Abstract #2919)) was the contribution of the instant inventors alone. As the Jacquemin et al. (Blood 92:710 (Abstract #2917)) or Gilles et al. (Blood 92:710 (Abstract #2919)) references are not prior art under 35 U.S.C. § 102, these references cannot be used as the basis of an obviousness rejection. The secondary references, U.S. Patent No. 6,602,015, Owens et al. (1994), and U.S. Patent No. 6,127,337, cannot support these rejections alone, and the rejection of claims 50, 53, 54, and 56 may be withdrawn.

CONCLUSION

Applicants submit that this case is now in condition for allowance, and such action is respectfully requested. If the Office does not concur, an interview with the undersigned is hereby requested.

Enclosed is a petition to extend the period of replying for one month, to and including April 15, 2005. Also enclosed is a Notice of Appeal, in which Applicants respectfully appeal the final rejection of the pending claims.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 15 April 2005

James D. DeCamp, Ph.D.
Reg. No. 43,580

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

Amendments to the drawings:

The attached sheets of drawings include changes to Figs. 6-9. These sheets replace the original sheets, Figs. 6-9. In Figs. 6-9, sequence identifiers have been added.

FIG. 6

VH BO 2C11

```
1/1                                                31/11
atg gac tgg acc tgg agg atc ctc ttc ttg gtg gca gca gct aca ggc acc cac gcc cag
Met asp trp thr trp arg ile leu phe leu val ala ala ala thr gly thr his ala gln

61/21                                              91/31
gtc caa ctg gta cag tct ggg gct gag gtg aag aag cct ggg gcc tca gtg aag gtc tcc
val gln leu val gln ser gly ala glu val lys lys pro gly ala ser val lys val ser

121/41                                             151/51
tgc aag gtt tcc gga tac acc ctc act gaa tta ccc gtg cac tgg gtc gga cag gct cct
cys lys val ser gly tyr thr leu thr glu leu pro val his trp val gly gln ala pro
             <----------------CDR 1----------------->

181/61                                             211/71
gga aaa ggg ctt gag tgg gtg gga agt ttt gat cct gaa agt gga gaa tca atc tac gca
gly lys gly leu glu trp val gly ser phe asp pro glu ser gly glu ser ile tyr ala
                         <-------------------------CDR 2-----------------. . .

241/81                                             271/91
cgg gag ttc cag ggc agc gtc acc atg acc gcg gac aca tct aca gac ata gcc tac atg
arg glu phe gln gly ser val thr met thr ala asp thr ser thr asp ile ala tyr met
---------------------->

301/101                                            331/111
gag ctg agc agc ctg aga tct gac gac acg gcc gtg tat tac tgt gca gtc cct gac cct
glu leu ser ser leu arg ser asp asp thr ala val tyr tyr cys ala val pro asp pro
                                                    | <---------- - - - - -

361/121                                            391/131
gat gct ttt gat atc tgg ggc caa ggg aca atg gtc acc gtc tct tca gcc tcc acc aag
asp ala phe asp ile trp gly gln gly thr met val thr val ser ser ala ser thr lys
--CDR 3---------->

421/141
ggc cca tcg gtc ttc ccc ctg gga tcc cgt(SEQ ID NO:5)
gly pro ser val phe pro leu gly ser arg(SEQ ID NO:6)
```

------- SEQUENCE IDENTIFIERS HAVE BEEN ADDED

FIG. 7

VL BO 2C11

```
1/1                                                 31/11
atg gaa acc cca gct cag ctt ctc ttc ctc ctg cta ctc tgg ctc cca gat acc acc gga
Met glu thr pro ala gln leu leu phe leu leu leu leu trp leu pro asp thr thr gly

61/21                                               91/31
gaa att gcg ttg acg cag tct cca ggc acc ctg tct ttg tct cca ggg gaa aga gcc acc
glu ile ala leu thr gln ser pro gly thr leu ser leu ser pro gly glu arg ala thr

121/41                                              151/51
ctc tcc tgc agg gcc agt cag agt ttt agc agc agc tac tta gcc tgg tat cag cag aaa
leu ser cys arg ala ser gln ser phe ser ser ser tyr leu ala trp tyr gln gln lys
          <------------------CDR 1----------------------->

181/61                                              211/71
cct ggc cag gct ccc agg ctc ctc atc tat ggt gca tcc acc agg gcc act ggc atc cca
pro gly gln ala pro arg leu leu ile tyr gly ala ser thr arg ala thr gly ile pro
                                    <----------CDR 2----------->

241/81                                              271/91
gac agg ttc agt ggc agt ggg tct ggg aca gac ttc act ctc acc atc agc aga ctg gag
asp arg phe ser gly ser gly ser gly thr asp phe thr leu thr ile ser arg leu glu

301/101                                             331/111
cct gaa gat ttt gca gtg tat tac tgt cag aag tat ggt acg tca gcg atc acc ttc ggg
pro glu asp phe ala val tyr tyr cys gln lys tyr gly thr ser ala ile thr phe gly
                                  <-------------CDR 3---------------->

361/121                                             391/131
caa ggg aca cga ctg gag att aaa gga act gtg gct gca cca tct gtc ttc atc ttc ccg
gln gly thr arg leu glu ile lys gly thr val ala ala pro ser val phe ile phe pro

421/141
cca tct(SEQ ID NO:6)
pro ser(SEQ ID NO:3)
```

------ SEQUENCE IDENTIFIERS HAVE BEEN ADDED

FIG. 8

VH Krix-1

```
1/1                                                 31/11
ATG GAC TGG ACC TGG AGG ATC CTC TTC TTG GTG GCA GCA GCC ACA GGA GCC CAC TCC CAG
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly Ala His Ser Gln

61/21                                               91/31
GTG CAA CTG GTG CAA TCT GGG GCT GAG GTG AAG AAG CCT GGG GCC TCA GTG AAG GTC TCC
Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser

121/41                                              151/51
TGC AAG ACC TCT GGA TAC AAC TTC ACC GGC TAC TCT GCT TCT GGA CAT ATC TTC ACC GCC
Cys Lys Thr Ser Gly Tyr Asn Phe Thr Gly Tyr Ser Ala Ser Gly His Ile Phe Thr Ala
    <-----------------------------------------CDR1-------------------------------

181/61                                              211/71
TAC TCT GTG CAC TGG GTG CGA CAG GCC CCT GGA CAA GGG CTT GAG TGG ATG GGA AGG ATC
Tyr Ser Val His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Arg Ile
-------------->                                                          <-------

41/81                                               271/91
AAC CCT AAC AGT GGT GCC ACA GAC TAT GCA CAT AAA TTT CAG GGC AGG GTC ACC ATG TCC
Asn Pro Asn Ser Gly Ala Thr Asp Tyr Ala His Lys Phe Gln Gly Arg Val Thr Met Ser
----------CDR2---------------------------------------------------->

301/101                                             331/111
```

FIG. 8


```
AGG GAC ACG TCC ATC AGC ACA GCC TAC ATG GAA CTG AGC AGG CTG ACA TCT GAC GAC ACG
Arg Asp Thr Ser Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Thr Ser Asp Asp Thr

361/121                                        391/131
GCC ATG TAT TAC TGT GCG AGA GCC GAC AAC TAT TTC GAT ATT GTG ACT GGC TAT ACT TCT
Ala Met Tyr Tyr Cys Ala Arg Ala Asp Asn Tyr Phe Asp Ile Val Thr Gly Tyr Thr Ser
                          <----------------------------CDR3-----------------

421/141                                        451/151
CAT TAC TTT GAC TAC TGG GGC CGG GGA ACC CTG GTC ACC GTC TCC TCA (SEQ ID NO:7)
His Tyr Phe Asp Tyr Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser (SEQ ID NO:8)
------------------>
```

SEQUENCE IDENTIFIERS HAVE BEEN ADDED

FIG. 9

VL KRIX 1

```
1/1                                                 31/11
ATG GAA ACC CCA GCT CAG CTT CTC TTC CTC CTG CTA CTC TGG CTC CCA GAT ACC ACC GGA
Met glu thr pro ala gln leu leu phe leu leu leu leu trp leu pro asp thr thr gly

61/21                                               91/31
GAA ATT GTG TTG ACG CAG TTC CCA GGC ACC CTG TCT TTG TCT CCA GGG GAA AGA GCC ACC
glu ile val leu thr gln phe pro gly thr leu ser leu ser pro gly glu arg ala thr

121/41                                              151/51
CTC TCC TGC AGG GCC AGT CAG AGT GTT GCC AGC GCC TAC TTA GCC TGG TAC CAG CAA AAA
leu ser cys arg ala ser gln ser val ala ser ala tyr leu ala trp tyr gln gln lys
          <-------------------CDR 1---------------------->

181/61                                              211/71
CCT GGC CAG GCT CCC AGG CTC CTC ATC TAT GGT GCA TCC AGT AGG GCC ACC GAC ATC CCA
pro gly gln ala pro arg leu leu ile tyr gly ala ser ser arg ala thr asp ile pro
                                    <---------CDR 2----------->

241/81                                              271/91
CAC AGG TTC AGT GGC AGT GGG TCT GGG ACA GAC TTC ACT CTC ACC ATC AGC AGA CTG GAG
his arg phe ser gly ser gly ser gly thr asp phe thr leu thr ile ser arg leu glu

301/101                                             331/111
CCT GAA GAT TTT GCA GTG TAC TAC TGT CAG CAA TAT GGT ACC TCA GCC TTA CTC ACT TTC
pro glu asp phe ala val tyr tyr cys gln gln tyr gly thr ser ala leu leu thr phe
                                  <----------------CDR 3---------------->

361/121                                             391/131
GGC GGA GGG ACC AAG GTG GAG ATC AAA CGA ACT GTG GCT GCA CCA TCT GTC TTC ATC TTC
gly gly gly thr lys val glu ile lys arg thr val ala ala pro ser val phe ile phe

421/141
CCG CCA TCT(SEQ ID NO:4) ------- SEQUENCE IDENTIFIERS
pro pro ser(SEQ ID NO:1)        HAVE BEEN ADDED
```